From Pharmaceutical Substance to Product – An Industrial Perspective on Continuous Processing

CMAC Open Day
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Overview of Presentation

- Challenges of continuous processing in the pharmaceutical industry
- Continuous processing in AstraZeneca
- Drug substance
  - Flow chemistry
  - Equipment
- Continuous crystallisation
- Drug product
  - Wet granulation
- Conclusions
- Acknowledgements
Continuous Processing in the Pharmaceutical Industry

A unique challenge?

• **Attrition**
  - Only a small percentage of what R&D work on is commercialised.
  - Capital Investment – existing facilities and supply chains, return on investment
  - Gaps in what we know; the science and traditional skills

• **Regulation**
  - The industry is highly regulated, risk averse and conservative.
  - Culture, ‘It’s not how we do things around here’

• **The Product**
  - A safe, efficacious, differentiated (and increasingly reimbursable) clinical outcome, not the medicine itself.
  - Focus of R&D investment

• These challenge the adoption of new manufacturing methodologies and technologies.
AZ Journey

• GOAL – to design and use continuous processes to generate value for the business throughout the lifecycle of the product.
• Different challenges in the different areas need different solutions
  - Outsourced API manufacture
  - Historically low investment in linking substance properties and product performance.
  - Internal, Global formulated product manufacture
• Winning hearts and minds
  - Overcoming techno-economic barriers
  - Addressing skills gaps
  - Changing culture
Continuous Processing in AZ
Built on collaboration

Measurement, analysis and control

API Process Development and Manufacture
Identify, understand, implement and exploit continuous processing where it adds tangible benefits

Particle Engineering
Design and deliver the right API particles

Drug Product Process Development and Manufacture
Replace wet granulation with continuous dry granulation

COLLABORATION across industry and academia is an ESSENTIAL element of the AZ strategy.

• Academics more able to deliver fundamental science allowing industry to focus on application and methodologies. Key that real or good model compounds are used.
• Industrial collaboration in this precompetitive area supports knowledge sharing, leverages investment and strengthens internal and external influence.
• Key overcoming inertia and resistance to change.
Drug Substance
Benefits of Reactions in Flow

Why?
• Selectivity
• Safety
  • unstable/difficult to handle reagents
  • Reactive/explosive intermediates
• Critical mixing control
• Highly exothermic/endothermic reactions
• Excess temperatures
  • Cryogenic or high temperatures
• Unstable products/substrates
• Precise reaction times

Challenges
• Solids block flow reactors
• Work-up in batch may be a bottle-neck
  • Telescopes, liquid/liquid separations, continuous distillation, SMB chromatography

If the manufacture is not going well the process can be stopped and starting materials preserved – not possible in batch!
Example 1: Curtius reaction
A Safer More Efficient Process

• Delivered 700g at 85% yield
• Laboratory delivered (non GMP)
• Safer chemistry, enabling better control of hazardous reagents

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{O} & \quad + & \quad - & \quad \text{N}
\end{align*}
\begin{array}{c}
\text{heat} \\
\text{-N}_2(\text{g})
\end{array}
\Rightarrow \quad \text{R} \quad \text{N} \quad \text{C} \quad \text{O}
\]
Example 2: Nitration
Green chemistry example

- Developed flow chemistry in <2 weeks
- Huge, process intensification
- Removed need for chlorinated solvent
- Solvent free reaction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Batch</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rxn time</td>
<td>4 to 16 hours</td>
<td>30 to 60 seconds</td>
</tr>
<tr>
<td>Nitric Acid</td>
<td>Comparable equivalents</td>
<td></td>
</tr>
<tr>
<td>Solvent</td>
<td>5.2 rel vols</td>
<td>None (neat acid)</td>
</tr>
<tr>
<td>Conversion</td>
<td>Comparable</td>
<td></td>
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</table>
Equipment & Technology
New Lab Equipment

Karr Extraction Column
Centrifugal Extractor
Gas Membrane Reactor

Improving Laboratory Capability

Work Up
Reaction
Flow Chemistry Scale-Up

• GMP modular continuous processing equipment installed in LSL (Macc)

• Alfa Laval continuous flow reactor used to deliver early phase material:
  • 1 kg processed in 7 hours
  • 74% yield (vs 60% batch)
  • Improved quality

Continuous processing enables new operating conditions to be exploited
Crystallisation
Benefits of Crystallisation in Flow

- Batch to batch, campaign to campaign consistency in particle properties
  - ‘same particles as last time’
- Increased quality
- Variable ‘batch size’
- Faster
- Leaner
- Avoid milling and micronising by achieving tighter control over particle size
- Control over particle size, shape and agglomeration
Crystallisation in a COBR

**Continuous**
- Material moves continually through the equipment

**Oscillatory**
- Although there is a net flow through the unit, the local flow moves back and forth

**Baffled**
- Small baffles are installed along the length to promote turbulence and hence mixing

**Reactor**
- Or crystalliser, or extractor, or…

- Mixing is controlled by oscillations, not the net flow as in the case of turbulent flows
- Plug flow characteristics are obtained in laminar flows
- This allows significantly shorter length of reactor and much compact reactor setup than conventional systems
Process Description

- Crude API is dissolved in solvent at reflux
- Heat to reflux and hold for dissolution
- Agitate and cool the flask contents by 20°C
- Hold
- Reduce the agitation speed and cool to 10°C
- Hold
- Total cycle time 9 hours 40 minutes
- Concentration of the order of 0.062kg/litre (or 6.2g/100ml)
Screening Trials
Batch

- Aim to identify key parameters for crystallisation of model API
  - $dT/dt; X_{o,f}; C$
- Carried out batch uni-variate experiments
  - Investigate key parameters
  - Would do FED in the future
    - More efficient use of resources
## Screening Trials

### Batch

<table>
<thead>
<tr>
<th>Oscillation displacement</th>
<th>Oscillation frequency</th>
<th>Baffle Spacing</th>
<th>Mixing</th>
</tr>
</thead>
<tbody>
<tr>
<td>API Concentration</td>
<td>Use of Seed</td>
<td></td>
<td>Solution Chemistry</td>
</tr>
<tr>
<td>Cooling rate</td>
<td>Hold time for nucleation</td>
<td></td>
<td>Temperature</td>
</tr>
</tbody>
</table>

- Oscillation displacement
- Oscillation frequency
- Baffle Spacing
- Mixing
- Solution Chemistry
- Temperature
Screening Trials
Continuous Flow

Aim to create particles of a defined size

<table>
<thead>
<tr>
<th>Target</th>
<th>Cooling</th>
<th>Agitation</th>
<th>Concentration</th>
<th>Seeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>Fast</td>
<td>High</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Large rods</td>
<td>Slow 0.25°C</td>
<td>Low</td>
<td>Std</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>min⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>Fast</td>
<td>Low</td>
<td>Std</td>
<td>None</td>
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<tr>
<td>Agglomerates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid size</td>
<td>1°C min⁻¹</td>
<td>Std</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Small</td>
<td>Fast</td>
<td>High</td>
<td>High</td>
<td>1%w/w @ 70°C</td>
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</tbody>
</table>
1°C/min

57°C
47°C
33°C
20°C
10°C
3°C/min seeded

57°C

37°C

10°C after 5 mins
5°C/min seeded

57°C

33°C

10°C no hold

10°C 5 min hold
Aggregation or Agglomeration?

- Lasentec and microscopy data suggest that model API crystals form aggregates/agglomerates, even when seeded
- These aggregates/agglomerates appear to be broken down when a hold period is incorporated i.e. any crystalline bridges between the primary particles are not yet completely desolvated and cemented
- Any bonds that are formed can therefore be relatively easily broken by agitation
Product Performance

5°C/min

Compressible

Incompressible

1°C/min
Product Performance

- All continuously generated material filters very well
- Agglomerated/ aggregated material appears compressible
- Rods appear relatively uncompresible following cake consolidation
Drug Product
Benefits of Continuous Wet Granulation

• Cost, time and material saving throughout the product life-cycle

  - More experiments in less time with less drug substance leading to greater accrual of knowledge and consequent increases in process control and robustness

  - Greater flexibility of batch size leading to reduced inventories and fewer issues of scale-up

  - Increased yield through fewer losses during processing

  - Smaller footprint with reduced infrastructure and energy costs

  - Potential for real-time release and reduced analytical costs
Early Observations

• Potential for rapid prototyping and process evaluation
• Partial process understanding
  • Impact of screw configuration and water quantity, throughput and screw speed
• Some differences in process and product attributes experienced between batch and continuous processes
• Rapid scale-up achievable by extending processing time
  • Stabilisation of the process critical to flexibility in batch size
Process Understanding: Continuous vs Batch
Granule analysis: Particle size analysis (sieve)
• Long disintegration times
• Steep response → Denser granules?
General process observations across products

- Water Quantity
  - particle size ↑
  - flowability ↑
  - weight variation ↓
  - dissolution ↓

- Screw Speed
  - particle size ↓
  - weight variation ↑

- Feed Rate
  - particle size ↑
Concluding Remarks
More than just a technical challenge ...

Substantial momentum gained and on the road to adoption of continuous processes in the Pharmaceutical industry

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<th>Understanding</th>
<th>Capability</th>
<th>Availability</th>
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<th>Delivery Risk</th>
<th>Existing Assets</th>
<th>Campaigns</th>
<th>Timelines</th>
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Culture of cross functional collaboration and innovation

“A major cultural change is required on behalf of chemists, engineers and managers and it is this, rather than technical difficulty which represents the main obstacle to progress”.

Amy Robertson | 12th September 2013
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